

Quinine

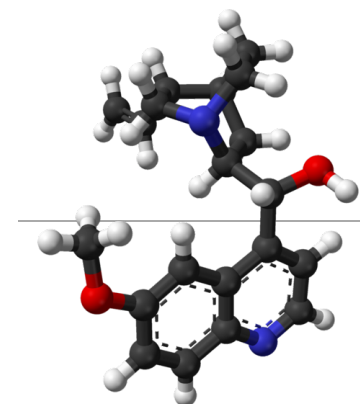
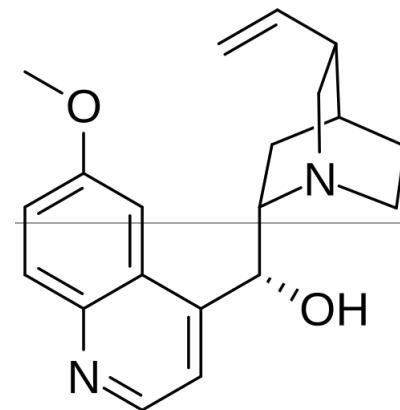
Quinine is a medication used to treat malaria and babesiosis.^[4] This includes the treatment of malaria due to *Plasmodium falciparum* that is resistant to chloroquine when artesunate is not available.^{[4][5]} While sometimes used for nocturnal leg cramps, quinine is not recommended for this purpose due to the risk of serious side effects.^[4] It can be taken by mouth or intravenously.^[4] Malaria resistance to quinine occurs in certain areas of the world.^[6] Quinine is also used as an ingredient in tonic water and other beverages to impart a bitter taste.^[7]

Common side effects include headache, ringing in the ears, vision issues, and sweating.^[4] More severe side effects include deafness, low blood platelets, and an irregular heartbeat.^[4] Use can make one more prone to sunburn.^[4] While it is unclear if use during pregnancy carries potential for fetal harm, treating malaria during pregnancy with quinine when appropriate is still recommended.^[4] Quinine is an alkaloid, a naturally occurring chemical compound. It possesses a C₉H₇N quinoline functional group (pyridine fused to benzene).^[4]

Quinine was first isolated in 1820 from the bark of a cinchona tree, which is native to Peru,^{[4][8][9]} and its molecular formula was determined by Adolph Strecker in 1854.^[10] The class of chemical compounds to which it belongs is thus called the cinchona alkaloids. Bark extracts had been used to treat malaria since at least 1632 and it was introduced to Spain as early as 1636 by Jesuit missionaries returning from the New World.^[11] It is on the World Health Organization's List of Essential Medicines.^[12] Treatment of malaria with quinine marks the first known use of a chemical compound to treat an infectious disease.^[13]

Uses

Quinine



Clinical data

Pronunciation	US: /ˈkwɪnaɪn/, /kwɪˈniːn/ or UK: /ˈkwɪniːn/ <i>KWIN-een</i>
Trade names	Qualaquin, Quinbisul, others ^[1]

Medical

As of 2006, quinine is no longer recommended by the World Health Organization (WHO) as a first-line treatment for malaria, because there are other substances that are equally effective with fewer side effects. They recommend that it be used only when artemisinins are not available.^{[14][15][16][17]} Quinine is also used to treat lupus and arthritis.

Quinine was frequently prescribed as an off-label treatment for leg cramps at night, but this has become less common since 2010 due to a warning from the US Food and Drug Administration (FDA) that such practice is associated with life-threatening side effects.^{[18][19][20]} Quinine can also act as a competitive inhibitor of monoamine oxidase (MAO), an enzyme that removes neurotransmitters from the brain. As an MAO inhibitor, it has potential to serve as a treatment for individuals with psychological disorders, similar to antidepressants that inhibit MAO.^[21]

Available forms

Quinine is a basic amine and is usually provided as a salt. Various existing preparations include the hydrochloride, dihydrochloride, sulfate, bisulfate and gluconate. In the United States, quinine sulfate is commercially available in 324 mg tablets under the brand name Qualaquin.

All quinine salts may be given orally or intravenously (IV); quinine gluconate may also be given intramuscularly (IM) or rectally (PR).^{[22][23]} The main problem with rectal administration is that the dose can be expelled before it is completely absorbed; in practice, this is corrected by giving a further half dose. No injectable preparation of quinine is licensed in the US; quinidine is used instead.^{[24][25]}

<u>AHFS/ Drugs.com</u>	Monograph (https://www.drugs.com/monograph/quinine-sulfate.html)
<u>MedlinePlus</u>	a682322 (https://medlineplus.gov/druginfo/meds/a682322.html)
<u>License data</u>	<u>US</u> <u>DailyMed</u>: <u>Quinine</u> (https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=Quinine) <u>US</u> <u>FDA</u>: <u>Quinine</u> (https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&SearchTerm=Quinine&SearchType=BasicSearch)
<u>Pregnancy category</u>	<u>AU</u> : D ^[2]
<u>Routes of administration</u>	By mouth, <u>intramuscular</u> , <u>intravenous</u> , <u>rectal</u>
<u>ATC code</u>	M09AA01 (<u>WHO</u> (https://www.whooc.no/atc_ddd_index/?code=M09AA01)) P01BC01 (<u>WHO</u> (https://www.whooc.no/atc_ddd_index/?code=P01BC01))
<u>Legal status</u>	Legal status <u>AU</u>: S4 (Prescription only) <u>CA</u>: R-only <u>UK</u>: POM (Prescription only) <u>US</u>: R-only

Quinine base in various salts	
Name	Amount equivalent to 100 mg quinine base
Quinine base	100 mg
Quinine bisulfate	169 mg
Quinine dihydrochloride	122 mg
Quinine gluconate	160 mg
Quinine hydrochloride	111 mg
Quinine sulfate dihydrate [(quinine) ₂ H ₂ SO ₄ ·2H ₂ O]	121 mg

Beverages

Quinine is a flavor component of tonic water and bitter lemon soft drinks. On the soda gun behind many bars, tonic water is designated by the letter "Q" representing quinine.^[26]

Tonic water was initially marketed as a means of delivering quinine to consumers in order to offer anti-malarial protection. According to tradition, because of the bitter taste of anti-malarial quinine tonic, British colonials in India mixed it with gin to make it more palatable, thus creating the gin and tonic cocktail, which is still popular today.^[27] While it is possible to drink enough tonic water to temporarily achieve quinine levels that offer anti-malarial protection, it is not a sustainable long-term means of protection.^[28]

In France, quinine is an ingredient of an *apéritif* known as *quinquina*, or "*Cap Corse*", and the wine-based *apéritif* Dubonnet. In Spain, quinine (also known as "Peruvian bark" for its origin from the native cinchona tree) is sometimes blended into sweet Malaga wine, which is then called "*Malaga Quina*". In Italy, the traditional flavoured wine Barolo Chinato is infused with quinine and local herbs, and is served as a *digestif*. In Britain, the company A.G. Barr uses quinine as an ingredient in the carbonated and caffeinated beverage Irn-Bru. In Uruguay and Argentina, quinine is an ingredient of a PepsiCo tonic water named Paso de los Toros. In Denmark, it is used as an ingredient in the carbonated sports drink Faxe Kondi made by Royal Unibrew.

Pharmacokinetic data	
Protein binding	70–95% ^[3]
Metabolism	Liver (mostly <u>CYP3A4</u> and <u>CYP2C19</u> -mediated)
Elimination half-life	8–14 hours (adults), 6–12 hours (children) ^[3]
Excretion	Kidney (20%)
Identifiers	
IUPAC name	
CAS Number	130-95-0 (https://commonchemistry.cas.org/detail?cas_rn=130-95-0) ✓
PubChem CID	8549 (https://pubchem.ncbi.nlm.nih.gov/compound/8549)
IUPHAR/BPS	2510 (https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=2510)
DrugBank	DB00468 (https://www.drugbank.ca/drugs/DB00468) ✓
ChemSpider	84989 (https://www.chemspider.com/Chemical-Structure.84989.html) ✓
UNII	A7V27PHC7A (https://precision.fda.gov/uniisearch/srs/unii/A7V27PHC7A)
KEGG	D08460 (https://www.kegg.jp/entry/D08460) ✓
ChEBI	CHEBI:15854 (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=15854)

As a flavouring agent in drinks, quinine is limited to 83 ppm (83 mg/L) in the United States,^{[29][30]} to 85 mg/L in Taiwan,^[31] and to 100 mg/L in the European Union.^{[32][33]}

Direct use of cinchona bark in beverages is also allowed in the US, with a maximum allowed total cinchona alkaloid level of 83 ppm in the finished beverage.^[34]

Scientific

Quinine (and quinidine) are used as the chiral moiety for the ligands used in Sharpless asymmetric dihydroxylation as well as for numerous other chiral catalyst backbones. Because of its relatively constant and well-known fluorescence quantum yield, quinine is used in photochemistry as a common fluorescence standard.^{[35][36]}

Contraindications

Because of the narrow difference between its therapeutic and toxic effects, quinine is a common cause of drug-induced disorders, including thrombocytopenia and thrombotic microangiopathy.^[37] Even from minor levels occurring in common beverages, quinine can have severe adverse effects involving multiple organ systems, among which are immune system effects and fever, hypotension, hemolytic anemia, acute kidney injury, liver toxicity, and blindness.^[37] In people with atrial fibrillation, conduction defects, or heart block, quinine can cause heart arrhythmias, and should be avoided.^[38]

Quinine can cause hemolysis in G6PD deficiency (an inherited deficiency), but this risk is small and the physician should not hesitate to use quinine in people with G6PD deficiency when there is no alternative.^[39]

While not necessarily an absolute contraindication, concomitant administration of quinine with drugs primarily metabolized by CYP2D6 may lead to higher than expected plasma concentrations of the drug, due to quinine's strong inhibition of the enzyme.^[40]

ChEMBL	bild=ChEMBL:15854 ✖ ChEMBL170 (https://www.ebi.ac.uk/chembl/explore/compound/ChEMBL170) ✓
CompTox Dashboard (EPA)	DTXSID0044280 (https://comptox.epa.gov/dashboard/chemical/details/DTXSID0044280)
ECHA InfoCard	100.004.550 (https://echa.europa.eu/substance-information/-/substanceinfo/100.004.550)
Chemical and physical data	
Formula	C ₂₀ H ₂₄ N ₂ O ₂
Molar mass	324.424 g·mol ^{−1}
3D model (JSmol)	Interactive image (https://chemapps.stolaf.edu/jmol/jmol.php?model=%5BH%5D%5BC%40%40%5D1%28%5BC%40%40H%5D%28C2%3DCC%3DC3%3DCC%3DC%28C%3DC23%29OC%29O%29C%5BC%40%40H%5D4CC%5BN%40%5D1C%5BC%40%40H%5D4C%3DC)
Melting point	177 °C (351 °F)
SMILES	
InChI	✖✓ (what is this?) (verify)

Adverse effects

Quinine can cause unpredictable serious and life-threatening blood and cardiovascular reactions including low platelet count and hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP), long QT syndrome and other serious cardiac arrhythmias including *torsades de pointes*, blackwater fever, disseminated intravascular coagulation, leukopenia, and neutropenia.^[4] Some people who have developed TTP due to quinine have gone on to develop kidney failure.^{[4][39]} It can also cause serious hypersensitivity reactions including anaphylactic shock, urticaria, serious skin rashes, including Stevens–Johnson syndrome and toxic epidermal necrolysis, angioedema, facial edema, bronchospasm, granulomatous hepatitis, and itchiness.^{[4][39]}

The most common adverse effects involve a group of symptoms called cinchonism, which can include headache, vasodilation and sweating, nausea, tinnitus, hearing impairment, vertigo or dizziness, blurred vision, and disturbance in color perception.^{[4][37][39]} More severe cinchonism includes vomiting, diarrhea, abdominal pain, deafness, blindness, and disturbances in heart rhythms.^[39] Cinchonism is much less common when quinine is given by mouth, but oral quinine is not well tolerated (quinine is exceedingly bitter and many people will vomit after ingesting quinine tablets).^[4] Other drugs, such as Fansidar (sulfadoxine with pyrimethamine) or Malarone (proguanil with atovaquone), are often used when oral therapy is required. Quinine ethyl carbonate (quinine etabonate) is tasteless and odourless,^[41] but is available commercially only in Japan. Blood glucose, electrolyte and cardiac monitoring are not necessary when quinine is given by mouth.

Quinine has diverse unwanted interactions with numerous prescription drugs, such as potentiating the anticoagulant effects of warfarin.^[4] It is a strong inhibitor of CYP2D6,^[40] an enzyme involved in the metabolism of many drugs.

Mechanism of action

Quinine is used for its toxicity to the malarial pathogen, *Plasmodium falciparum*, by interfering with its ability to dissolve and metabolize hemoglobin.^{[4][42]} As with other quinoline antimalarial drugs, the precise mechanism of action of quinine has not been fully resolved, although in vitro studies indicate it inhibits nucleic acid and protein synthesis, and inhibits glycolysis in *P. falciparum*.^[4] The most widely accepted hypothesis of its action is based on the well-studied and closely related quinoline drug, chloroquine. This model involves the inhibition of hemozoin biocrystallization in the heme detoxification pathway, which facilitates the



Tonic water, in normal light and ultraviolet "black light". The quinine content of tonic water causes it to fluoresce under black light.

aggregation of cytotoxic heme. Free cytotoxic heme accumulates in the parasites, causing their deaths.^[6] Quinine may target the malaria purine nucleoside phosphorylase enzyme.^[43]

Chemistry

The UV absorption of quinine peaks around 350 nm (in UVA). Fluorescent emission peaks at around 460 nm (bright blue/cyan hue).^[44] Quinine is highly fluorescent (quantum yield ~0.58) in 0.1 M sulfuric acid solution.^{[35][36]}

Synthesis

Cinchona trees remain the only economically practical source of quinine. However, under wartime pressure during World War II, research towards its synthetic production was undertaken. A formal chemical synthesis was accomplished in 1944 by American chemists R.B. Woodward and W.E. Doering.^[45] Since then, several more efficient quinine total syntheses have been achieved,^[46] but none of them can compete in economic terms with isolation of the alkaloid from natural sources. The first synthetic organic dye, mauveine, was discovered by William Henry Perkin in 1856 while he was attempting to synthesize quinine.

Biosynthesis

In the first step of quinine biosynthesis, the enzyme strictosidine synthase catalyzes a stereoselective Pictet–Spengler reaction between tryptamine and secologanin to yield strictosidine.^{[47][48]} Suitable modification of strictosidine leads to an aldehyde. Hydrolysis and decarboxylation would initially remove one carbon from the iridoid portion and produce corynantheal. Then the tryptamine side-chain were cleaved adjacent to the nitrogen, and this nitrogen was then bonded to the acetaldehyde function to yield cinchonaminal. Ring opening in the indole heterocyclic ring could generate new amine and keto functions. The new quinoline heterocycle would then be formed by combining this amine with the aldehyde produced in the tryptamine side-chain cleavage, giving cinchonidinone. For the last step, hydroxylation and methylation gives quinine.^{[49][50]}

Catalysis

Quinine and other *Cinchona* alkaloids can be used as catalysts for stereoselective reactions in organic synthesis.^[51] Table 3B Plate 560 For example, the quinine-catalyzed Michael addition of a malononitrile to α,β-enones gives a high degree of stereochemical control.^[51]

History

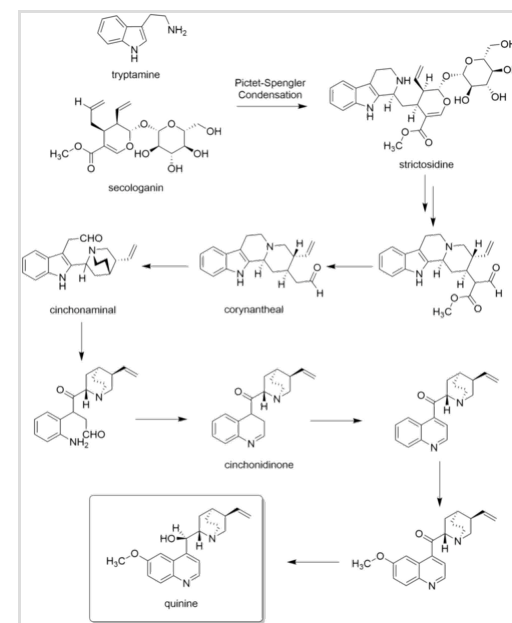
Quinine was used as a muscle relaxant by the Quechua people, who are indigenous to Peru, Bolivia and Ecuador, to halt shivering.^[52] The Quechua would mix the ground bark of cinchona trees with sweetened water to offset the bark's bitter taste, thus producing something similar to tonic water.^[53]

Spanish Jesuit missionaries were the first to bring cinchona to Europe. The Spanish had observed the Quechua's use of cinchona and were aware of the medicinal properties of cinchona bark by the 1570s or earlier: Nicolás Monardes (1571) and Juan Fragoso (1572) both described a tree, which was subsequently identified as the cinchona tree, whose bark was used to produce a drink to treat diarrhea.^[54] Quinine has been used in unextracted form by Europeans since at least the early 17th century.^[55]

A popular story of how it was brought to Europe by the Countess of Chinchon was debunked by medical historian Alec Haggis around 1941.^[56] During the 17th century, malaria was endemic to the swamps and marshes surrounding the city of Rome. It had caused the deaths of several popes, many cardinals and countless common Roman citizens. Most of the Catholic priests trained in Rome had seen malaria patients and were familiar with the shivering brought on by the febrile phase of the disease.

The Jesuit Agostino Salumbrino (1564–1642),^[57] an apothecary by training who lived in Lima (now in present-day Peru), observed the Quechua using the bark of the cinchona tree to treat such shivering. While its effect in treating malaria (and malaria-induced shivering) was unrelated to its effect in controlling shivering from rigors, it was a successful medicine against malaria. At the first opportunity, Salumbrino sent a small quantity to Rome for testing as a malaria treatment.^[58] In the years that followed, cinchona bark, known as Jesuit's bark or Peruvian bark, became one of the most valuable commodities shipped from Peru to Europe. When King Charles II was cured of malaria at the end of the 17th Century with quinine, it became popular in London.^[59] It remained the antimalarial drug of choice until the 1940s, when other drugs took over.^[60]

The form of quinine most effective in treating malaria was found by Charles Marie de La Condamine in 1737.^{[61][62]} In 1820, French researchers Pierre Joseph Pelletier and Joseph Bienaimé Caventou first isolated quinine from the bark of a tree in the genus Cinchona – probably Cinchona pubescens – and subsequently named the substance.^[63] The name was derived from the original Quechua (Inca) word for the cinchona tree bark, *quina* or *quina-quina*, which means "bark of bark" or "holy bark". Prior to 1820, the bark was dried, ground to a fine powder, and mixed into a liquid (commonly wine) in order to be drunk. Large-scale use of quinine as



Quinine biosynthesis

a malaria prophylaxis started around 1850. In 1853 Paul Briquet published a brief history and discussion of the literature on "quinquina".^[64]

Quinine played a significant role in the colonization of Africa by Europeans. The availability of quinine for treatment had been said to be the prime reason Africa ceased to be known as the "white man's grave". A historian said, "it was quinine's efficacy that gave colonists fresh opportunities to swarm into the Gold Coast, Nigeria and other parts of west Africa".^[65]

To maintain their monopoly on cinchona bark, Peru and surrounding countries began outlawing the export of cinchona seeds and saplings in the early 19th century. In 1865, Manuel Incra Mamani collected seeds from a plant particularly high in quinine and provided them to Charles Ledger. Ledger sent them to his brother, who sold them to the Dutch government. Mamani was arrested on a seed collecting trip in 1871, and beaten so severely, likely because of providing the seeds to foreigners, that he died soon afterwards.^[66]

By the late 19th century the Dutch grew the plants in Indonesian plantations. Soon they became the main suppliers of the tree. In 1913 they set up the Kina Bureau, a cartel of cinchona producers charged with controlling price and production.^[67] By the 1930s Dutch plantations in Java were producing 22 million pounds of cinchona bark, or 97% of the world's quinine production.^[65] U.S. attempts to prosecute the Kina Bureau proved unsuccessful.^[67]

During World War II, Allied powers were cut off from their supply of quinine when Germany conquered the Netherlands, and Japan controlled the Philippines and Indonesia. The US had obtained four million cinchona seeds from the Philippines and began operating cinchona plantations in Costa Rica. Additionally, they began harvesting wild cinchona bark during the Cinchona Missions. Such supplies came too late. Tens of thousands of US troops in Africa and the South Pacific died of malaria due to the lack of quinine.^[65] Despite controlling the supply, the Japanese did not make effective use of quinine, and thousands of Japanese troops in the southwest Pacific died as a result.^{[68][69][70][71]}

Quinine remained the antimalarial drug of choice until after World War II. Since then, other drugs that have fewer side effects, such as chloroquine, have largely replaced it.^[72]

Bromo Quinine were brand name cold tablets containing quinine, manufactured by Grove Laboratories. They were first marketed in 1889 and available until at least the 1960s.^[73]



19th-century illustration of *Cinchona calisaya*

Conducting research in central Missouri, John S. Sappington independently developed an anti-malaria pill from quinine. Sappington began importing cinchona bark from Peru in 1820. In 1832, using quinine derived from the cinchona bark, Sappington developed a pill to treat a variety of fevers, such as scarlet fever, yellow fever, and influenza in addition to malaria. These illnesses were widespread in the Missouri and Mississippi valleys. He manufactured and sold "Dr. Sappington's Anti-Fever Pills" across Missouri. Demand became so great that within three years, Sappington founded a company known as Sappington and Sons to sell his pills nationwide.^[74]

Society and culture

Natural occurrence

The bark of *Remijia* contains 0.5–2% of quinine. The bark is cheaper than bark of *Cinchona*. As it has an intense taste, it is used for making tonic water.^[75]

Regulation in the US

From 1969 to 1992, the US Food and Drug Administration (FDA) received 157 reports of health problems related to quinine use, including 23 which had resulted in death.^[76] In 1994, the FDA banned the marketing of over-the-counter quinine as a treatment for nocturnal leg cramps. Pfizer Pharmaceuticals had been selling the brand name Legatrin for this purpose. It is also sold as a softgel (by SmithKlineBeecham) as Q-vel. Doctors may still prescribe quinine, but the FDA has ordered firms to stop marketing unapproved drug products containing quinine. The FDA is also cautioning consumers about off-label use of quinine to treat leg cramps.^{[18][19]} Quinine is approved for treatment of malaria, but was also commonly prescribed to treat leg cramps and similar conditions. Because malaria is life-threatening, the risks associated with quinine use are considered acceptable when used to treat that condition.^[77]

Though Legatrin was banned by the FDA for the treatment of leg cramps, the drug manufacturer URL Mutual has branded a quinine-containing drug named Qualaquin. It is marketed as a treatment for malaria and is sold in the United States only by prescription. In 2004, the CDC reported only 1,347 confirmed cases of malaria in the United States.^[78]

Abortion

For much of the 20th century, women's use of an overdose of quinine to deliberately terminate a pregnancy was a relatively common abortion method in various parts of the world, including China.^[79]

Cutting agent

Quinine is sometimes detected as a cutting agent in street drugs such as cocaine and heroin.^[80]

Other animals

Quinine is used as a treatment for *Cryptocaryon irritans* (commonly referred to as white spot, crypto or marine ich) infection of marine aquarium fish.^[81]

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gentian: it has in its taste a considerable astringency, with some aromaticity, because at the end of chewing it, one breathes with a sweet odor. The Indians hold this bark in high regard, and use it for all sorts of diarrhea, that are with blood [i.e., bloody] and without it. The Spanish [who are] tired of this disease, on the advice of the Indians, have used this bark and have healed many of those with it. They take as much as a small bean, make [it into] powder, take it in red wine or in appropriate water, if they have fever or illness: it must be taken in the morning on an empty stomach, three or four times: otherwise, using the order and regimen that suits those who have diarrhea.]

- Fragoso J (1572). *Discursos de las cosas aromaticas, arboles y frutales, y de otras muchas medicinas simples que se traen de la India Oriental y que sirven al uso de medicina* (<https://books.google.com/books?id=ZGplEb3BRfAC>) [*Discourse on fragrant things, trees and fruits, as well as many other ordinary medicines that have been brought from India and the Orient and are of use to medicine*] (in Spanish). Madrid, Spain: Francisco Sánchez. p. 35. "En el nuevo mundo ay un grande arbol que lleva las hojas a forma de coraçon, y carece de fruto. Tiene dos cortezas, la una gruessa muy solida y dura, que assi en la sustancia como en el color es muy semejante al Guayacan: la otra es mas delgada y blanquezina, la qual es amarga con alguna estipticidad: y demas desto es aromatica. Tienenla en mucho nuestros Indios, porque la usan contra qualesquier camaras, tomando del polvo peso de una drama o poco mas, desatado en agua azerada, o vino tinto." [In the new world, there is a big tree that bears leaves in the form of a heart, and lacks fruit. It has two barks, one [is] thick, very solid, [and] hard, which in substance as well as in color is much like *guayacan* [i.e., *lignum vitae*]: the other is thinner and whitish, which is bitter with some styptic [i.e., astringent] quality: and besides this, it is aromatic. Our Indians regard it highly, because they use it against any diarrheas, taking a weight of a dram or a bit more of the powder, mixing it in mineral water, or red wine.]
- 55. Achan J, Talisuna AO, Erhart A, Yeka A, Tibenderana JK, Baliraine FN, et al. (May 2011). "Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria" (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3121651>). *Malaria Journal*. **10** 144. doi:10.1186/1475-2875-10-144 (<https://doi.org/10.1186%2F1475-2875-10-144>). PMC 3121651 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3121651>). PMID 21609473 (<https://pubmed.ncbi.nlm.nih.gov/21609473>)
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- 57. de Andrade A (3 August 1642). "Vida del Devoto Hermano Agustin Salumbrino" [The life of the devout Brother Agustin Salumbrino]. *Varones ilustres en santidad, letras y zelo de las almas de la Compañía de Jesús* (<https://books.google.com/books?id=paalyIGye1gC&pg=PA612>) [*Illustrious men in holiness, letters, and zeal for souls of the Society of Jesus*]. Varones ilustres de la Compañía de Jesús (in Spanish). Vol. 5. Original series by Juan Eusebio Nieremberg. Madrid, Spain: José Fernandez de Buendía (published 1666). pp. 612–628. p. 612: "Nació el Hermano Agustin Salumbrino el año de mil y quinientos y sesenta y quatro en la Ciudad de Fłorì en la Romania [...]" [Brother Agustino Salumbrino was born in the year 1564 in the city of Forlì in Romagna]

58. See:

- Medina Rodríguez F, Aceves Ávila FJ, Moreno Rodríguez J (2007). "Precisions on the History of Quinine" (<https://www.reumatologiaclinica.org/en-pdf-S2173574307702460>). *Reumatología Clínica*. Letters to the Editor. **3** (4): 194–196. doi:10.1016/S2173-5743(07)70246-0 (<https://doi.org/10.1016%2FS2173-5743%2807%2970246-0>). ISSN 2173-5743 (<https://search.worldcat.org/issn/2173-5743>). "In fact, though the last word on this has not yet been spoken, there are Jesuit texts that mention that quinine reached Rome in 1632, with the provincial of the Jesuit missions in Peru, father Alonso Messia Venegas, as its introducer, when he brought a sample of the bark to present it as a primacy, and who had left Lima 2 years earlier, because evidence of his stay in Seville 1632 has been registered, publishing one of his books there and following his way to Rome as a procurator."
 - Torres Saldamando E (June 1882). "El P. Diego de Torres Vazquez" (<https://archive.org/details/losantiguosjesui00tor/page/180/mode/2up>). *Los antiguos jesuitas del Perú* (in Spanish). Lima, Peru: Imprenta Liberal. pp. 180–181. p. 181: "Al siguiente año se dirigieron á Europa los Procuradores P. Alonso Messía Venegas y P. Hernando de Leon Garavito, llevando gran cantidad de la corteza de la quina, cuyo conocimiento extendieron por el mundo los jesuitas." [In the following year [i.e., 1631] there went to Europe the procurators Father Alonso Messia Venegas and Father Hernando de Leon Garavito, taking a great quantity of cinchona bark, knowledge of which the Jesuits spread throughout the world.]
 - Bailetti A. "Capítulo 10: La Condesa de Chinchón" (<http://amalariayelarboldequina.blogspot.com/2013/11/capitulo-9-proximamente.html>). *LA MISIÓN DEL JESUITA AGUSTÍN SALUMBRINO, la malaria y el árbol de quina*. "A últimas horas de la tarde del treinta y uno de mayo de 1631 se hizo a la vela la Armada Real con dirección a Panamá llevando el precioso cargamento de oro y plata. En una de las naves viajaban los procuradores jesuitas padres Alonso Messia y Hernando León Garavito custodiando los fardos con la corteza de quina en polvo preparados por Salumbrino. Después de casi veinte días de navegación el inapreciable medicamento llegó a la ciudad de Panamá, donde fue descargado para cruzar en mulas el agreste camino del istmo palúdico hasta Portobelo para seguir a Cartagena y la Habana, cruzar el Atlántico y llegar a Sanlúcar de Barrameda en Sevilla. [...] Finalmente siguió su camino a Roma y a su destino final el Hospital del Espíritu Santo." [Late in the afternoon of 31 May 1631, the royal armada set sail in the direction of Panama, carrying its multimillion [dollar] cargo of gold and silver. On one of the ships traveled the Jesuit procurators Fathers Alonso Messia and Hernando León Garavito, guarding the cases of powdered cinchona bark, prepared by Salumbrino. After almost 20 days of sailing, medicine arrived in the city of Panama, where it was transloaded onto mules. It then traveled the malarial isthmus as far as Portobelo, thence to Cartagena [in Colombia] and Havana. It then traveled to Sanlúcar de Barrameda in Seville, [Spain]. [...] Finally it followed the road to Rome and to its final destination, the Hospital of the Holy Spirit]
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External links

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 - Quinine (<https://www.inchem.org/documents/pims/pharm/pim464.htm>) at the International Programme on Chemical Safety
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